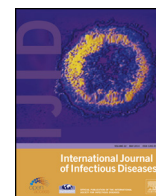


Contents lists available at [ScienceDirect](http://ScienceDirect.com)

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries ☆☆☆

Tatiana M. Lanzieri^a, Sheila C. Dollard^{a,*}, Stephanie R. Bialek^a, Scott D. Grosse^b^a National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA^b National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

ARTICLE INFO

Article history:

Received 25 September 2013

Received in revised form 12 November 2013

Accepted 7 December 2013

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

Cytomegalovirus

Congenital infection

Prevalence

Developing countries

SUMMARY

Background: Congenital cytomegalovirus (CMV) infection is the leading infectious cause of congenital hearing loss and neurodevelopmental disability in developed countries. Information on congenital CMV infection in developing countries appears to be lacking.**Methods:** We conducted a systematic literature review to identify studies from developing countries with population-based samples of at least 300 infants that used laboratory methods established as reliable for the diagnosis of congenital CMV infection.**Results:** Most studies were excluded due to biased samples or inadequate diagnostic methods; consequently the search identified just 11 studies that were from Africa, Asia, and Latin America. The number of newborns tested ranged from 317 to 12 195. Maternal CMV seroprevalence ranged from 84% to 100%. CMV birth prevalence varied from 0.6% to 6.1%. CMV-associated impairments were not documented in most studies.**Conclusions:** Birth prevalence ranges were higher than for Europe and North America, as expected based on the higher maternal CMV seroprevalence. With very limited data available on sequelae, the disease burden of congenital CMV in developing countries remains largely unknown at this time.

Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.

Open access under [CC BY-NC-ND license](http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Human cytomegalovirus (CMV) is a member of the herpesvirus family and one of the most ubiquitous viruses in humans. Congenital CMV infection occurs when virus from the mother crosses the placenta and infects the immunologically immature fetus. The consequences or sequelae of congenital CMV infection include fetal death, infant death, and neurological and sensory impairments.^{1,2} During pregnancy, women may have either a primary (first) CMV infection or non-primary infection, in which a previously infected woman experiences reactivation of a latent virus or re-infection with a new viral strain. The frequency of vertical transmission and severity of the outcome is reported to be much greater for primary maternal infection;³ however, non-

primary infection is more common than primary infections and thus likely contributes more total cases of congenital CMV infection and related disability.^{4–6}

The prevalence of congenital CMV infection has been reported to vary from approximately 0.2% to 2% (average 0.65%), with higher overall rates in countries with higher maternal seroprevalence.^{7,8} Most of these estimates come from studies conducted in Europe, the USA, and Japan. In developing countries, the reported prevalence of congenital CMV infection varies substantially, both within and between countries, with some reported prevalences as high as 6–14%.^{9,10} Higher birth prevalences combined with additional stresses on infant health in developing countries could augment disability from congenital CMV infection. We conducted a systematic review of the literature to identify population-based studies from developing countries that evaluated congenital CMV infection birth prevalence, and where available sequelae, using methods that are considered reliable for the evaluation of congenital CMV infection.

2. Methods

We identified studies published prior to May 2013 that reported the birth prevalence of congenital CMV infection by

☆☆ Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author.

E-mail address: sdollard@cdc.gov (S.C. Dollard).

searching PubMed/MEDLINE, Embase/Ovid, LILACS, SciELO, BioMed Central, and CABDirect databases using the keywords CMV, HCMV, cytomegalovirus, human cytomegalovirus, congenital, infant, neonate, newborn, incidence, and prevalence, with no restrictions on language. We restricted the search to articles from countries in Africa, the Americas, Caribbean Region, Central America, Latin America, South America, Asia, Atlantic Islands, and Indian Ocean Islands. We excluded articles from the USA, Canada, Japan, Australia, and Europe, and articles focused on HIV infection. Articles were flagged if the title or abstract indicated that the study reported the birth prevalence of congenital CMV infection in countries classified as developing by the International Monetary Fund.¹¹ Two studies were included that were from countries currently not categorized as developing, but which were considered developing when the studies were conducted (Taiwan 1996; Republic of Korea 1992).¹¹ We also reviewed citations in the articles from our search to identify any additional relevant articles not captured by the database searches. We reviewed titles and abstracts from the resulting group of citations and selected articles that reported the birth prevalence of CMV.

Among selected articles, we reviewed the full text to identify studies meeting the following criteria: original peer-reviewed studies with either a cohort or cross-sectional design, a population-based sample of at least 300 newborns, diagnosis of congenital CMV infection by detection of virus by culture or viral DNA by PCR from infant urine or saliva collected within 3 weeks of birth.^{12,13}

We excluded studies using CMV IgM-based screening because of the low sensitivity of IgM for the detection of congenital infection^{14,15} and highly variable performance among commercial tests.^{16,17} In the case of multiple reports from the same authors with overlapping study dates, we included the most recent or most comprehensive report. We excluded studies limited to maternal populations with an elevated risk of transmitting congenital CMV infection, such as mothers with recent primary CMV infection or HIV infection. We also excluded studies with infant populations

selected for clinical signs of congenital CMV infection or hospitalization in neonatal intensive care units.

For each of the studies that met the above criteria we extracted the following information: maternal demographics and CMV seroprevalence; methods used for CMV newborn screening (types of clinical specimen, time to specimen collection following birth, laboratory methods); number of newborns tested for and positive for congenital CMV infection; number of congenitally infected newborns who were symptomatic at birth, as assessed by the individual studies since criteria for defining symptomatic congenital CMV disease varied across studies and in some studies was not defined. The quality of individual studies was assessed by evaluating sample size, risk of bias in the study population, and the laboratory methods. We calculated the confidence intervals for the birth prevalence estimates and, to assess the heterogeneity across the studies, we calculated the I^2 statistic, which indicates the proportion of total variation across studies that is due to heterogeneity (e.g., likely to arise from true differences in prevalence, study quality, inclusion criteria, laboratory methods) rather than chance.¹⁸ Analyses were performed using Comprehensive Meta Analysis Version 2.2.064 (Biostat, Englewood, NJ, USA).

3. Results

Of a total of 564 citations identified, 84 met criteria for full-text assessment, of which 11 met criteria for inclusion in this review. Of the 73 studies excluded after full-text assessment, 55 (46%) had a sample size less than 300 newborns, 52 (44%) had biased populations that over-represented mothers with primary CMV infection or symptomatic newborns, and 34 (29%) used exclusively CMV IgM-based screening; 44 (71%) were excluded for more than one of the above reasons. Of the 11 studies included in this review, two were conducted in Africa (Ivory Coast¹⁹ and Gambia²⁰), four in Asia (Korea,²¹ Taiwan,²² China,¹⁰ and India²³), and five in Latin America (Chile,²⁴ Brazil,^{25,26} Mexico,²⁷ and Panama²⁸) (Table 1).

Table 1
Summary of methods and results from studies assessing birth prevalence of congenital CMV infection in developing countries

First author and year of publication	Country and time period	Maternal seroprevalence	Newborn screening			Number of newborns with congenital CMV (%)		
			Clinical specimens	Laboratory methods	Tested	Infected		Symptomatic
						n	Prevalence, % (95% CI)	
Schopfer 1978 ¹⁹	Ivory Coast	100%	Urine	Culture	2032	28	1.4 (1.0–2.0)	0 (0)
van der Sande 2007 ²⁰	Gambia ^a 2002–2005	100% ^b	Urine	PCR	741	40	5.4 (4.0–7.3)	3 (8)
Sohn 1992 ²¹	Korea 1989–1991	96% ^b	Urine and cord blood	Culture	514	6	1.2 (0.5–2.6)	0 (0)
Tsai 1996 ²²	Taiwan ^a –	90%	Urine	Culture, PCR	1000	18	1.8 (1.1–2.8)	2 (11)
Zhang 2007 ¹⁰	China 1997–2000	92–99%	Urine	PCR	1159	71	6.1 (4.9–7.7)	17 (24)
Dar 2008 ²³	India –	99% ^b	Saliva, urine ^c	PCR	423	9	2.1 (1.1–4.0)	1 (11)
Luchsinger 1996 ²⁴	Chile 1989–1994	98%	Urine and saliva	Culture, PCR	658	12	1.8 (1.0–3.2)	0 (0)
Weirich 1997 ²⁵	Brazil 1994–1995	90% ^b	Saliva	Culture	663	21	3.2 (2.1–4.8)	6 (29)
Yamamoto 2011 ²⁶	Brazil 2003–2009	96%	Urine and/or saliva	PCR, culture ^c	12 195	121	1.0 (0.8–1.2)	12 (10)
Noyola 2003 ²⁷	Mexico ^a 2001	92%	Saliva	Culture	560	5	0.9 (0.4–2.1)	0 (0)
Estripeaut 2007 ²⁸	Panama 2003–2004	84% ^b	Urine	PCR	317	2	0.6 (0.2–2.5)	1 (50)

CMV, cytomegalovirus; CI, confidence interval.

^a Studies that were conducted in well-baby nurseries or excluded severely ill newborns.

^b Mothers tested as part of the study.

^c Indicates specimen or method used for confirmation.

Six studies were published after the year 2000, four in the 1990s, and one in 1978. The duration of enrollment for the studies varied from 3 months to 6 years. Four were cross-sectional studies and seven were cohort studies.

The number of newborns tested for congenital CMV infection varied from 317 to 12 195; seven out of 11 studies had <1000 newborns tested. Three of the 11 studies excluded some categories of ill newborns from screening: the study from Gambia excluded newborns that were preterm or had serious congenital deficits; the study from Taiwan screened only newborns who were 'essentially healthy' at birth; and the study from Mexico was limited to newborns from the well-baby nursery. Clinical specimens were collected within 3 days of birth in nine studies and within 1 or 2 weeks of birth in the remaining studies. Five studies relied exclusively on PCR for the detection of CMV. Our quality assessment indicated a high risk of bias for all studies except for the Yamamoto study from Brazil.²⁶

The birth prevalence of congenital CMV infection varied from 0.6% in Panama to 6.1% in China (Table 1). The I^2 value was 95%, indicating considerable heterogeneity across the studies, therefore we did not combine the studies to estimate an average birth prevalence of congenital CMV infection.

Criteria used to define infected newborns as symptomatic varied across studies. All newborns with congenital CMV infection received a physical examination at birth. More thorough assessment with head imaging, audiological, ophthalmological, and/or neurological examinations was performed in three studies.^{22,26,28} The proportion of newborns with congenital CMV infection classified as symptomatic at birth in studies with >15 infected newborns varied from 0% in four of the studies^{19,21,24,27} to 29% in the Weirich study from Brazil.²⁵ Studies conducted in Mexico and Gambia that excluded some categories of ill infants reported 8–11% of infected newborns had symptomatic infection.^{20,27} The Yamamoto study from Brazil included a precise case definition of symptomatic congenital CMV disease based on the presence of at least one of the following: petechiae, cholestatic jaundice (conjugated bilirubin level >2 mg/dl), hepatosplenomegaly, purpura, microcephaly, seizures, chorioretinitis, or abnormal cranial computerized tomography (CT) findings.²⁶ In that study, 12 (10%) of 121 newborns with congenital CMV infection were classified as symptomatic, three of whom had only abnormal cranial CT findings. However, the proportion of symptomatic infants would have increased to 22% if intrauterine growth restriction had also been included as a criterion of symptomatic congenital CMV disease, which it often is.

All studies reported maternal seroprevalence $\geq 90\%$, except the study from Panama in which maternal seroprevalence was 84%; mothers were tested directly for CMV IgG antibody in five studies.^{20,21,23,25,28} Among six studies that reported maternal demographic information, mothers of infected newborns were younger^{20,21,24,25,27} and more likely to be primigravidae or primiparae^{20,24,27,28} than mothers of uninfected newborns. In the study from India, the median number of children among mothers of infected newborns was one (range one to two) compared to two (range one to six) among mothers of uninfected newborns.²³ In contrast, the study from Ivory Coast reported similar distributions of maternal age and parity for newborns with and without congenital CMV infection.¹⁹

4. Discussion

Our systematic review of the literature on congenital CMV infection in developing countries identified 11 population-based studies using laboratory methods that are established as reliable for identifying congenital CMV infection. The CMV birth rates ranged from 0.6% to 6.1%, which is higher than the range of

0.2–2.0% (average of 0.65%) most often reported for developed countries,^{7,8} although the extent to which the selected studies are representative of other developing countries is not known. More studies are needed to understand the burden of disease associated with congenital CMV infection in these populations and how it may be affected by other prevalent conditions such as HIV infection, malnutrition, and malaria.

We found substantial variability across studies in the criteria used to define symptomatic congenital CMV infection, which is the main recognized predictor of permanent sequelae from CMV infection.⁸ Based on data from developed countries, an estimated 40–58% of newborns with symptomatic congenital CMV infection at birth will have permanent neurodevelopmental disabilities.⁸ Of studies we reviewed that had at least 15 infants with congenital CMV infection, the proportion classified as symptomatic was 0–29%, which is similar to estimates of 5–20% from studies in developed countries.⁸ Some of the criteria used to identify symptomatic CMV infection may be problematic when applied to developing countries. For example, intrauterine growth retardation is often associated with congenital CMV,^{2,29,30} but it is more common and less specific to CMV in developing countries given its association with maternal socioeconomic and nutritional factors, chronic diseases, and the use of drugs.³¹ Abnormal cranial CT findings are associated with congenital CMV infection and long-term sequelae,³² but CT scans cannot be performed routinely in limited-resource settings, and infants with congenital CMV infection presenting with central nervous system involvement may be more likely to remain undiagnosed in the newborn period.

Conditions for specimen collection, processing, and testing can be suboptimal in developing countries and cause laboratory results to be less accurate. Two reports with the highest rates of congenital CMV infection (5.4% in Gambia²⁰ and 6.1% in China¹⁰) relied exclusively on PCR methods. Other reports using PCR that did not meet our inclusion criteria reported higher CMV birth prevalences of 10–20%. Due to the extreme sensitivity of diagnostic PCR, false-positive results can occur in laboratories that do not have extensive expertise and quality control³³ and may result in artificially high estimates of CMV birth prevalence. High quality diagnostics also rely on specimen transport and storage at cold temperatures that are harder to maintain in areas with weaker infrastructure and inconsistent power supplies.

Findings from the countries included in our review are not necessarily representative of that country or region. The results from Gambia and Ivory Coast may not be generalizable to other regions in Africa with significantly different HIV prevalence, since CMV is more readily transmitted in the setting of HIV infection.^{34,35} Also, five of the studies were conducted two decades or longer ago and it is likely that living conditions have since changed. High seroprevalence is associated with lower socioeconomic status and crowding, which may have increased or decreased in some regions, altering patterns of CMV infection. This is especially true with very large, socioeconomically dynamic countries like China, India, and Brazil, where birth prevalences may vary substantially from region to region and by sociodemographic characteristics. A study from 1985 by Pannuti et al.³⁶ screened two groups of approximately 500 newborns for CMV by viral culture with results similar to other studies. The Pannuti study was not included in our analysis to avoid over-representation of any given population, because their sample was from the same region of Brazil as the 2011 study by Yamamoto²⁶ with 12 195 newborns screened.

CMV seroprevalence in developing countries is generally over 90% by adolescence and over 95% by early adulthood. Consequently most cases of congenital CMV infection result from non-primary maternal infection. By comparison, the CMV seroprevalence among 12–40-year-olds is 40–60% in the USA,³⁷ where both primary and non-primary maternal infection contribute substantially to

congenital CMV infection.⁴ Distinguishing congenital CMV infections due to primary vs. non-primary maternal infection from one another is not easily done. Studying congenital CMV infection in regions with very high seroprevalence presents the opportunity to study outcomes in a population in which those are likely due almost entirely to non-primary infection. A meta-analysis by de Vries et al. reported that the pooled risk of hearing loss from seven studies conducted in Europe and the Americas was similar following primary or non-primary maternal CMV infection.⁶ In a study from Brazil, the frequency of hearing loss was reported to be 33% (1/3) following primary infection, 15% following non-primary infection (6/40), and 7% (3/42) for indeterminate infections.²⁶ Overall, 6% of 85 infected infants followed up for at least 12 months were diagnosed with bilateral moderate to profound sensorineural hearing loss.²⁶ The findings from Brazil suggest that the frequency of bilateral moderate to profound sensorineural hearing loss is similar to or higher than in high-income countries (3–5%),³⁸ despite a shorter length of follow-up in the Brazilian study. In general, data on the association of non-primary infections with outcomes of congenital CMV infection are lacking.

CMV-associated sequelae could potentially be augmented by other perinatal conditions common in developing countries, such as malnutrition, malaria, and other infections, especially HIV. These factors contribute to higher rates of prematurity and intrauterine growth restriction, which have an impact on neonatal mortality and long-term morbidity.³⁹ The study from Gambia included in our review found that the prevalence of congenital CMV infection was three-fold higher among infants born to mothers who had acute placental malaria infection.²⁰ Studies have shown that maternal HIV infection may increase the risk of vertical transmission of CMV, symptomatic disease, and long-term sequelae in infected infants, thus high HIV prevalence increases the overall burden of congenital CMV infection.^{34,35,40,41} In addition, adolescent pregnancy is more common in many developing countries and young maternal age is an established risk factor for congenital CMV infection. In this review, the association with young maternal age was present in five of six studies that recorded maternal age.

Our review has several limitations, the main one being the small number of papers that have been published on this subject. We observed a wide prevalence range across countries (0.6% in Panama²⁸ to 6.1% in China¹⁰) that could have resulted as much from different methods as from true differences in population prevalence. We made every attempt to identify studies that applied unselected or random screening of newborns, but many studies lacked clear descriptions of their study populations. Three of 11 studies either excluded infants who were 'seriously ill' or limited screening to the well-baby nursery, which could have caused an underestimate of CMV birth prevalence in those studies.

In conclusion, developing countries have some of the world's largest populations and highest birth rates, thus the aggregate number of children born with congenital CMV infection in these regions is likely to be enormous. Most congenital CMV infection in developing countries results from non-primary maternal infection, which is less understood as a cause of congenital CMV disease than primary maternal infection. The potential for vaccines and behavioral interventions⁴² to reduce non-primary infection and the associated burden of disease is unknown. There is especially a need for research on the potential for other health stresses in developing countries to augment mortality and morbidity of congenital CMV infection. Studies that test unselected populations of newborns for CMV using established methods, and that evaluate the infants at birth and for at least a few years after birth, may not be feasible in many developing countries, but could be a goal if and when resources become available. At the present time no effective interventions to interrupt the transmission of congenital CMV can

be recommended for such populations, however, clinicians should be aware of both the ubiquity and risk of CMV infection in pregnancy.

Funding source: No external funding was used for this study.

Conflict of interest: The authors have no conflicts of interest.

References

- Enders G, Bader U, Lindemann L, Schalasta G, Daiminger A. Prenatal diagnosis of congenital cytomegalovirus infection in 189 pregnancies with known outcome. *Prenat Diagn* 2001;**21**:362–77.
- Boppana SB, Pass RF, Britt WJ, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. *Pediatr Infect Dis J* 1992;**11**:93–9.
- Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med* 1992;**326**:663–7.
- Wang C, Zhang X, Bialek S, Cannon MJ. Attribution of congenital cytomegalovirus infection to primary versus non-primary maternal infection. *Clin Infect Dis* 2011;**52**:e11–3.
- Mussi-Pinhata MM, Yamamoto AY, Moura Brito RM, de Lima Isaac M, de Carvalho e Oliveira PF, Boppana S, et al. Birth prevalence and natural history of congenital cytomegalovirus infection in a highly seroimmune population. *Clin Infect Dis* 2009;**49**:522–8.
- de Vries JJ, van Zwet EW, Dekker FW, Kroes AC, Verkerk PH, Vossen AC. The apparent paradox of maternal seropositivity as a risk factor for congenital cytomegalovirus infection: a population-based prediction model. *Rev Med Virol* 2013;**23**:241–9.
- Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol* 2007;**17**:253–76.
- Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol* 2007;**17**:355–63.
- Bello C, Whittle H. Cytomegalovirus infection in Gambian mothers and their babies. *J Clin Pathol* 1991;**44**:366–9.
- Zhang XW, Li F, Yu XW, Shi XW, Shi J, Zhang JP. Physical and intellectual development in children with asymptomatic congenital cytomegalovirus infection: a longitudinal cohort study in Qinba mountain area, China. *J Clin Virol* 2007;**40**:180–5.
- Nielsen L. Classifications of countries based on their level of development: how it is done and how it could be done. International Monetary Fund Working Paper. Washington, DC: IMF; 2011.
- Revello MG, Gerna G. Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. *Clin Microbiol Rev* 2002;**15**:680–715.
- Lazzarotto T, Guerra B, Lanari M, Gabrielli L, Landini MP. New advances in the diagnosis of congenital cytomegalovirus infection. *J Clin Virol* 2008;**41**:192–7.
- Stagno S, Tinker MK, Elrod C, Fuccillo DA, Cloud G, O'Beirne AJ. Immunoglobulin M antibodies detected by enzyme-linked immunosorbent assay and radioimmunoassay in the diagnosis of cytomegalovirus infections in pregnant women and newborn infants. *J Clin Microbiol* 1985;**21**:930–5.
- Halwachs-Baumann G, Genser B, Danda M, Engele H, Rosegger H, Folsch B, et al. Screening and diagnosis of congenital cytomegalovirus infection: a 5-y study. *Scand J Infect Dis* 2000;**32**:137–42.
- Lazzarotto T, Galli C, Pulvirenti R, Rescaldani R, Vezzo R, La Gioia A, et al. Evaluation of the Abbott AxSYM cytomegalovirus (CMV) immunoglobulin M (IgM) assay in conjunction with other CMV IgM tests and a CMV IgG avidity assay. *Clin Diagn Lab Immunol* 2001;**8**:196–8.
- Gentile M, Galli C, Pagnotti P, Di Marco P, Tzantzoglou S, Bellomi F, et al. Measurement of the sensitivity of different commercial assays in the diagnosis of CMV infection in pregnancy. *Eur J Clin Microbiol Infect Dis* 2009;**28**:977–81.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60.
- Schopfer K, Lauber E, Krech U. Congenital cytomegalovirus infection in newborn infants of mothers infected before pregnancy. *Arch Dis Child* 1978;**53**:536–9.
- van der Sande MA, Kaye S, Miles DJ, Waight P, Jeffries DJ, Ojuola OO, et al. Risk factors for and clinical outcome of congenital cytomegalovirus infection in a peri-urban West-African birth cohort. *PLoS One* 2007;**2**:e492.
- Sohn YM, Park KI, Lee C, Han DG, Lee WY. Congenital cytomegalovirus infection in Korean population with very high prevalence of maternal immunity. *J Korean Med Sci* 1992;**7**:47–51.
- Tsai CH, Tsai FJ, Shih YT, Wu SF, Liu SC, Tseng YH. Detection of congenital cytomegalovirus infection in Chinese newborn infants using polymerase chain reaction. *Acta Paediatr* 1996;**85**:1241–3.
- Dar L, Pati SK, Patro AR, Deorari AK, Rai S, Kant S, et al. Congenital cytomegalovirus infection in a highly seropositive semi-urban population in India. *Pediatr Infect Dis J* 2008;**27**:841–3.
- Luchsinger V, Suarez M, Schultz R, Barraza P, Guzman M, Terrada L, et al. [Incidence of congenital cytomegalovirus infection in newborn infants of different socioeconomic strata]. *Rev Med Chil* 1996;**124**:403–8.
- Weirich J. [Congenital cytomegalovirus infection: a study carried out in the "Fundacao Santa Casa de Misericordia do Para", Brazil]. *Rev Soc Bras Med Trop* 1998;**31**:325–6.

26. Yamamoto AY, Mussi-Pinhata MM, Isaac Mde L, Amaral FR, Carvalheiro CG, Aragon DC, et al. Congenital cytomegalovirus infection as a cause of sensorineural hearing loss in a highly immune population. *Pediatr Infect Dis J* 2011;**30**:1043–6.
27. Noyola DE, Mejia-Elizondo AR, Canseco-Lima JM, Allende-Carrera R, Hernandez-Salinas AE, Ramirez-Zacarias JL. Congenital cytomegalovirus infection in San Luis Potosi, Mexico. *Pediatr Infect Dis J* 2003;**22**:89–90.
28. Estripeaut D, Moreno Y, Ahumada Ruiz S, Martinez A, Racine JD, Saez-Llorens X. [Seroprevalence of cytomegalovirus infection in puerperal women and its impact on their newborns]. *An Pediatr (Barc)* 2007;**66**:135–9.
29. Ista AS, Demmler GJ, Dobbins JG, Stewart JA. Surveillance for congenital cytomegalovirus disease: a report from the National Congenital Cytomegalovirus Disease Registry. *Clin Infect Dis* 1995;**20**:665–70.
30. Williamson WD, Demmler GJ, Percy AK, Catlin FI. Progressive hearing loss in infants with asymptomatic congenital cytomegalovirus infection. *Pediatrics* 1992;**90**:862–6.
31. Sheridan C. Intrauterine growth restriction—diagnosis and management. *Aust Fam Physician* 2005;**34**:717–23.
32. Noyola DE, Demmler GJ, Nelson CT, Griesser C, Williamson WD, Atkins JT, et al., Houston Congenital CMV Longitudinal Study Group. Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *J Pediatr* 2001;**138**:325–31.
33. Espy MJ, Uhl JR, Sloan LM, Buckwalter SP, Jones MF, Vetter EA, et al. Real-time PCR in clinical microbiology: applications for routine laboratory testing. *Clin Microbiol Rev* 2006;**19**:165–256.
34. Doyle M, Atkins JT, Rivera-Matos IR. Congenital cytomegalovirus infection in infants infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J* 1996;**15**:1102–6.
35. Guibert G, Warszawski J, Le Chenadec J, Blanche S, Benmebarek Y, Mandelbrot L, et al., French Perinatal Cohort. Decreased risk of congenital cytomegalovirus infection in children born to HIV-1-infected mothers in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2009;**48**:1516–25.
36. Pannuti CS, Vilas-Boas LS, Angelo MJ, Carvalho RP, Segre CM. Congenital cytomegalovirus infection. Occurrence in two socioeconomically distinct populations of a developing country. *Rev Inst Med Trop Sao Paulo* 1985;**27**:105–7.
37. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988–2004. *Clin Infect Dis* 2010;**50**:1439–47.
38. Grosse SD, Ross DS, Dollard SC. Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment. *J Clin Virol* 2008;**41**:57–62.
39. Moss W, Darmstadt GL, Marsh DR, Black RE, Santosham M. Research priorities for the reduction of perinatal and neonatal morbidity and mortality in developing country communities. *J Perinatol* 2002;**22**:484–95.
40. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The “silent” global burden of congenital cytomegalovirus. *Clin Microbiol Rev* 2013;**26**:86–102.
41. Slyker JA, Lohman-Payne BL, John-Stewart GC, Maleche-Obimbo E, Emery S, Richardson B, et al. Acute cytomegalovirus infection in Kenyan HIV-infected infants. *AIDS* 2009;**23**:2173–81.
42. Vauloup-Fellous C, Picone O, Cordier AG, Parent-du-Chatelet I, Senat MV, Frydman R, et al. Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital. *J Clin Virol* 2009;**46**(Suppl 4):S49–53.